

REMARKS

Applicant respectfully requests reconsideration of the present application, in view of the foregoing amendments and the following remarks.

I. Status of Claims

Claims 1-7, 9-11, 15-26, 41-61 are pending upon the entry of this amendment. Claims 14 and 30-38 have been cancelled without prejudice or disclaimer.

Claims 50-61 have been added. Claims 51-53 have been added to define the alkaline conditions of the complex of claim 1 and 7, or in the method of claim 15. Claim 52 essentially corresponds to the cancelled claim 14. Support of the alkaline conditions prescribed in claims 51-53 can be found, for example, at page 3, lines 7-10, and page 12, Example 1 (page 12, lines 14-17 and page 13, lines 6-10). Claims 54 and 55 have been added to prescribe the pH of the composition of claims 46 and 48. Support of these claims can be found at page 10, lines 9-14.

Claims 56-61 have been added to claim a composition useful for inhibiting cariogenesis comprising a complex of claim 1. These claims are parallel to claims 46-49 and 54-55 that are directed to a composition comprising a complex of claim 7. Support of these claims can be found from the original claims 37-38 and page 10, lines 9-14.

Claims 1, 3-7, 9-11, 15, 25, 42, 43, 45-47 and 49 have been amended mainly to attend to the examiner's concerns, and further to define the subject matter more clearly. Applicant explains the amendments of claims in more detail below.

Applicant acknowledges that these amendments are made after *Ex parte* Quayle action. However, because the amendments neither introduce new matter nor raise new issues, and because the amendments place the application in condition for allowance, applicant respectfully requests the entry of these amendments.

II. Claim Amendments

Claims 1, 7 and 15

Applicant has amended claims 1, 7 and 15 to define the feature of the claimed invention more clearly by reciting that "amorphous calcium (fluoride) phosphate is formed in **alkaline conditions**."

As explained in the previous response filed April 12, 2001, the claimed invention is distinguished from the prior art in the use of the alkaline phase of calcium phosphate, *i.e.*, forming amorphous calcium phosphate under alkaline conditions. Calcium phosphate formed at acidic or neutral pH is known for its poor binding affinity to phosphopeptide and poor localization at the tooth surface. In contrast, amorphous phosphate that is formed under alkaline conditions provides the superior efficacy and binding ability. The specification articulates the importance of adjustment of pH to alkaline during the formation of calcium phosphate in the claimed invention. See page 3, lines 7-29. That is, the superior properties of the claimed invention result from the alkaline pH for the formation of calcium phosphate, not from the pH of the resultant complex.

Therefore, in an effort to clarify the key feature of the claimed invention that distinguishes it from the prior art, applicant has amended claims 1, 7 and 15 to prescribe the formation of amorphous calcium phosphate under alkaline pH. Applicant respectfully submits that claims 1, 7 and 15, as amended, still reflect the characteristics the examiner found patentable in the *Ex parte* Quayle action.

In addition, the amended claim 1 clearly prescribes that calcium phosphate is amorphous and is formed in alkaline conditions so that the claimed complex contains the same elements as the complex of claim 7, except for a fluoride ion. Claim 15 has been amended to recite the complex as prescribed in claim 7, including the formation of amorphous calcium phosphate in alkaline conditions. As a result, applicant believes that claim 15 as amended is directed to a method of the complex that is subgeneric to claim 7.

In view of the amendments of claims 1 and 15, applicant respectfully requests rejoinder of claims 1 and 15 together with their dependent claims in the examination of the elected claims.

Other Amendments

1. Claims 3-6 and 42 have been amended to depend from claim 1, rather than claim 2, 3, 5 or 12. Claim 3 has been further amended to recite a specific formula as described at page 4, lines 7 of the specification.

2. Claims 9-11 have been amended to depend from claim 7, rather than claim 41 or 9. Claim 9 has been further amended to recite a specific formula to attend to the examiner's concern. The formula can be found at page 4, lines 7 of the specification.

3. Claims 5 and 11 have been further amended to correct a typographical error in the sequence listing.

4. Claims 45 and 47 have been amended to depend from claim 44 and 46, respectively.

5. Claim 25 has been amended to cure the lack of antecedent basis and to be directed to "a method of inhibiting formation of dental caries" in an effort to address the examiner's concern.

6. Claims 46 and 47 have been amended to recite "delivery vehicle" and to delete " dentifrice." Support of this amendment can be found from the original claims 39 and 40.

In view of the foregoing, applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The examiner is invited to contact the undersigned by telephone if there are any issues that the examiner believes could be resolved through a further exchange.

Respectfully submitted,

Date 8 May 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Marked up rewritten claims:

1. (Three Times Amended) A stable soluble calcium phosphate complex comprising phosphopeptide-stabilized amorphous calcium fluoride phosphate [or a derivative thereof], wherein said phosphopeptide includes the amino acid sequence Ser(P)-Ser(P)-Ser(P)-Glu-Glu (SEQ ID NO: 5) and said amorphous calcium fluoride phosphate [or the derivative thereof] is formed in alkaline conditions.

3. (Amended) A complex according to claim [2 further including HPO₄] 1, wherein said amorphous calcium fluoride phosphate is of the approximate formula [Ca₃(PO₄)_{1.87}(HPO₄)_{0.2}(H₂O)_x], wherein $x \geq 1$.

4. (Three Times Amended) A complex according to claim [3] 1, wherein said phosphopeptide includes an amino acid sequence selected from the group consisting of:

(SEQ ID NO: 1) Gln⁵⁹-Met-Glu-Ala-Glu-Ser(P)-Ile-Ser(P)-Ser(P)-Ser(P)-Glu-Ile-Val-Pro-Asn-Ser(P)-Val-Glu-Gln-Lys⁷⁹[.] $\alpha_{s1}(59-79)$;

(SEQ ID NO: 2) Arg¹-Glu-Leu-Glu-Glu-Leu-Asn-Val-Pro-Gly-Glu-Ile-Val-Glu-Ser(P)-Leu-Ser(P)-Ser(P)-Ser(P)-Glu-Glu-Ser-Ile-Thr-Arg²⁵[.] $\beta(I-25)$;

(SEQ ID NO: 3) Asn⁴⁶-Ala-Asn-Glu-Glu-Glu-Tyr-Ser-Ile-Gly-Ser(P)-Ser(P)-Ser(P)-Glu-Glu-Ser(P)-Ala-Glu-Val-Ala-Thr-Glu-Glu-Val-Lys⁷⁰ $\alpha_{s2}(46-70)$; and

(SEQ ID NO: 4) Lys¹-Asn-Thr-Met-Glu-His-Val-Ser(P)-Ser(P)-Ser(P)-Glu-Glu-Ser-Ile-Ile-Ser(P)-Gln-Glu-Thr-Tyr-Lys²¹ $\alpha_{s2}(1-21)$.

5. (Twice Amended) A complex according to claim [3] 1, wherein said phosphopeptide includes the amino acid sequence (SEQ ID NO: 1):

Gln⁵⁹-Met-Glu-Ala-[Gelu] Glu-Ser(P)-Ile-Ser(P)-Ser(P)-Ser(P)-Glu-Ile-Val-Pro-Asn-Ser(P)-Val-Glu-Gln-Lys⁷⁹ $\alpha_{s1}(59-79)$.

6. (Twice Amended) A complex according to claim [5 having a] 1, wherein said alkaline conditions are pH of about 7.0 to about 9.0.

7. (Three Times Amended) A stable soluble [alkaline] calcium phosphate complex comprising phosphopeptide-stabilized amorphous calcium phosphate [or a derivative thereof] wherein said phosphopeptide includes the amino acid sequence Ser(P)-Ser(P)-Ser(P)-Glu-Glu (SEQ ID NO: 5) and said amorphous calcium phosphate [or the derivative thereof] is formed in alkaline conditions.

9. (Twice Amended) A complex according to claim [41] 7, wherein [the formula further includes $\text{HPO}_4^{(2-)}$] said amorphous calcium fluoride phosphate is of the approximate formula $[\text{Ca}_3(\text{PO}_4)_{4.1.87}(\text{HPO}_4)_{0.2}(\text{H}_2\text{O})_x]$, wherein $x \geq 1$.

10. (Three Times Amended) A complex according to claim [9] 7, wherein said phosphopeptide includes an amino acid sequence selected from the group consisting of:

- (SEQ ID NO: 1) Gln59-Met-Glu-Ala-Glu-Ser(P)-Ile-Ser(P)-Ser(P)-Ser(P)-Glu-Ile-Val-Pro-Asn-Ser(P)-Val-Glu-Gln-Lys79 as1(59-79);
- (SEQ ID NO: 2) Arg1-Glu-Leu-Glu-Glu-Leu-Asn-Val-Pro-Gly-Glu-Ile-Val-Glu-Ser(P)-Leu-Ser(P)-Ser(P)-Ser(P)-Glu-Glu-Ser-Ile-Thr-Arg25 b(1-25);
- (SEQ ID NO: 3) Asn46-Ala-Asn-Glu-Glu-Glu-Tyr-Ser-Ile-Gly-Ser(P)-Ser(P)-Ser(P)-Glu-Glu-Ser(P)-Ala-Glu-Val-Ala-Thr-Glu-Glu-Val-Lys70 as2(46-70); and
- (SEQ ID NO: 4) Lys1-Asn-Thr-Met-Glu-His-Val-Ser(P)-Ser(P)-Ser(P)-Glu-Glu-Ser-Ile-Ile-Ser(P)-Gln-Glu-Thr-Tyr-Lys21 as2(1-21).

11. (Three Times Amended) A complex according to claim [9] 7, wherein said phosphopeptide includes the amino acid sequence (SEQ ID NO: 1):

Gln⁵⁹-Met-Glu-Ala-[Glu] Glu-Ser(P)-Ile-Ser(P)-Ser(P)-Ser(P)-Glu-Ile-Val-Pro-Asn-Ser(P)-Val-Glu-Gln-Lys⁷⁹ α_{s1} (59-79).

15. (Three Times Amended) A method of producing a stable [alkaline] calcium phosphate complex [having a pH of about 9.0] comprising phosphopeptide-stabilized amorphous calcium phosphate wherein said phosphopeptide includes the

amino acid sequence Ser(P)-Ser(P)-Ser(P)-Glu-Glu (SEQ ID NO: 5) and said amorphous calcium phosphate is formed in alkaline conditions comprising the steps of:

- (i) obtaining an aqueous solution of a phosphopeptide which has a pH of above 7 up to about 9.0, wherein said phosphopeptide includes the amino acid sequence Ser(P)-Ser(P)-Ser(P)-Glu-Glu (SEQ ID NO: 5);
- (ii) admixing the solution of step (i) with solutions comprising calcium, and inorganic phosphate and optionally fluoride at a pH of above 7 up to about 9.0;
- (iii) filtering the mixture resulting from step (ii);
- (iv) drying the mixture of step (iii), and
- (v) isolating the stable [alkaline] calcium phosphate complex.

25. (Three Time Amended) A method of inhibiting formation of dental caries or tooth decay comprising administering a complex according to claim 7 to the teeth or gums of a subject in need [of such treatment] thereof.

42. (Amended) A complex according to claim [11] Z, which has the formula $[(PP)(CP)_8]_n$, wherein n is equal to or greater than 1, "PP" represents said phosphopeptide, and "CP" represents calcium phosphate.

43. (Amended) A complex according to claim 42, [which has the formula $[(PP)(CP)_8]_6$, wherein "PP" and "CP" are as defined in claim 42] wherein n is 6.

45. (Amended) The method of claim [48] 44, wherein said condition is osteoporosis or osteomalacia.

46. (Amended) A composition useful for inhibiting cariogenesis, comprising a [dentifrice] delivery vehicle and a complex according to claim 7 in an amount effective to inhibit cariogenesis.

47. (Amended) The composition of claim [44] 46, wherein said delivery vehicle is a dentifrice [is] selected from the group consisting of toothpaste, toothpowder, a liquid dentifrice, mouthwash, a troche, chewing gum, dental paste, gingival massage cream and a gargle tablets.

49. (Amended) The composition according to claim [46] 48, wherein said foodstuff is a dairy product.